Case Report

Recurrent staphylococcal abscess in an adolescent with hyperimmunoglobulin E syndrome: A rare presentation

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ABSTRACT

Hyperimmunoglobulin E syndrome (HIES) more commonly referred to as Job's syndrome, is an infrequent primary immunodeficiency disorder. It can be inherited either by autosomal dominant or recessive mode with each one having distinct varied clinical presentation. The distinguishing clinical features include recurrent infections, dermatitis, and elevated serum immunoglobulin E (IgE) levels. We report a case of an adolescent female who presented with recurrent staphylococcal infection with axillary lymphadenitis, positive family history, and abnormal facial features mainly broad forehead, facial asymmetry, and peripheral blood eosinophilia with significantly high serum IgE levels, suggestive of autosomal dominant HIES.

Key words: Abscess, Autosomal dominant, Hyperimmunoglobulin E syndrome, Immunoglobulin E level, Job's syndrome

The hyperimmunoglobulin E syndrome (HIES) is an uncommon primary immunodeficiency syndrome, with characteristic triad of frequent skin and sinopulmonary infections, eczema, and high serum immunoglobulin E (IgE) levels. It is also known as Job's syndrome or hyper-IgE recurrent infection syndrome (HIE) [1]. It is reported to occur in one in 1,000,000 population globally. However, exact incidence in Indian population is not available due to the rarity of this condition [1].

Davis *et al*. first described Job's syndrome in 1966 with reference to the Biblical Job, who had sore boils. Later, the syndrome was modified by Buckley *et al*. in 1972, with additional feature of elevated serum IgE levels [1]. With time, the spectrum of clinical manifestations of this syndrome has been elaborated to contain varied facial, musculoskeletal, neurological, rheumatological, vascular, and cardiac involvement along with recurrent soft-tissue infections. Mode of transmission of HIES is both autosomal dominant HIES (AD-HIES) and autosomal recessive HIES (AR-HIES) which lead to distinctive clinical profile and outcome. The AD-HIES is predominantly featured by pulmonary, rheumatological, and skeletal manifestations while the AR-HIES presents with distinct immunological manifestations, recurrent viral infections, and neurological impairment. AD-HIES is caused by mutation in signal transducer and activator of transcription-3 (STAT-3) gene and AR-HIES results from dedicator of cytokinesis 8 (DOCK8) gene mutations [1,2].

Herein, we are presenting a case of 17-year-old adolescent female who manifested with recurrent staphylococcal abscesses, significant family history, and abnormal facial profile with markedly elevated serum IgE levels. Interestingly, there was no eczema and sinopulmonary infection. This was a delayed presentation of HIES syndrome, probably AD-HIES.

CASE REPORT

A 17-year-old female, resident of rural area in sub-Himalayan region of North India, presented with the complaint of swelling in the left axilla for the past 8 days. The swelling gradually increased in size and was associated with fever for the past 5 days. Fever was not accompanied with chills or rigors and there was no specific diurnal variation. The axillary swelling was not associated with cough, weight loss, decreased appetite, or recurrent episodes of loose stools. The child had significant history of multiple (>5) episodes of suppurative infection of axillary lymph nodes. First episode was a year ago, when she presented with swelling in the left axillary region which enlarged rapidly necessitating incision and drainage in a regional health-care facility. The aspirate demonstrated methicillin-sensitive *Staphylococcus aureus* (MSSA).

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As per the sensitivity pattern, she was started on intravenous linezolid at a dose of 10 mg/kg, twice daily for the first 7 days followed by oral linezolid at a dose of 10 mg/kg, twice daily for the subsequent 7 days. Afterward, she had four more similar episodes involving both the axillary regions before reporting to us. Out of them, two required aspiration along with antibiotic therapy. Interestingly, there was growth of MSSA both the times. The child was asymptomatic in between the episodes.

On further evaluation, it was revealed that the child also had delayed eruption of secondary dentition. Parents revealed that the child had allergic manifestations in the form of shortness of breath along with noisy breathing during exposure to cold and dust. For these symptoms, she was advised intermittent metered dose inhaler (MDI) with levosalbutamol (50 µg as and when required) since the age of 5 years. These manifestations occurred intermittently and responded to the above therapy. However, the child was thriving well despite these symptoms. Father also had recurrent skin abscesses requiring frequent medical attention. However, he was managed in the regional health-care facility and genetic workup was not done.

This child was admitted in the pediatric inpatient ward for further investigations and treatment. At admission, she was febrile, tachycardic, and normotensive and had oxygen saturation of 98% on ambient air. There was no tachypnea and the systemic examination was unremarkable. The child had asymmetric facial profile, broad forehead, deep-seated eyes, a broad nasal bridge, plump nasal tip, and high arched palate with mild prognathism (Fig. 1 and 2).

She also had four retained primary teeth and hyperextensibility of joints. The growth was between the normal (as per the standard growth charts according to her age). Local examination revealed tender, fluctuant swelling of 2×2 cm in the left axilla, which was warm to touch, mobile, and non-matted. However, there was no generalized lymphadenopathy.

Initial diagnosis of bacterial axillary lymphadenitis was made and she was subjected to baseline investigations. Complete blood count revealed normal hemoglobin, mildly elevated total leukocyte count ($12.1\times10^3/\mu L$) with absolute eosinophil count of $1860/mm^3$ (normal: $350–500/mm^3$). Erythrocyte sedimentation rate, hepatic, and renal function tests were normal and sepsis workup was negative. The workup for tuberculosis and human immunodeficiency virus was also negative. Chest X-ray and ultrasound abdomen were conducted to look for hilar and abdominal lymphadenopathy, respectively, and both were normal. Based on the scoring system with clinical and laboratory tests designed by Grimbacher *et al*., index case had a score of 43 which would predict the possibility of HIES genotype (Table 1) [3].

The child was treated with intravenous antibiotics and aspiration of the axillary soft-tissue abscess was done. There was thick, purulent material on aspiration which was sent for bacterial culture and mycobacterial culture including Ziehl–Neelsen stain and cartridge-based nucleic acid amplification test. The culture from the aspirate revealed growth of MSSA sensitive to

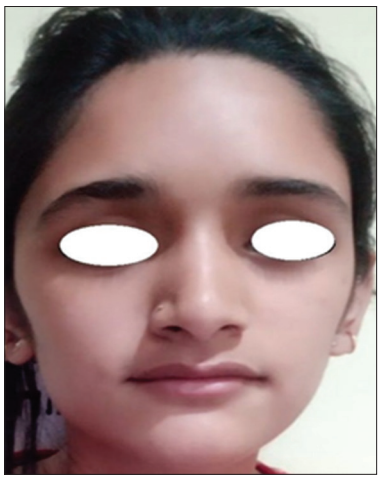

Figure 1: Facial profile of the patient showing asymmetry, broad forehead, deep-seated eyes, a broad nasal bridge, plump nasal tip

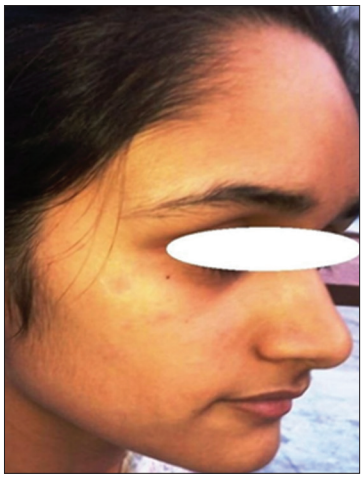

Figure 2: Side facial view of the patient showing broad forehead and mild prognathism

Table 1: Index case clinical and laboratory tests as per the scoring system for hyperimmunoglobulin E syndrome genotype

Clinical/laboratory parameter	In index case	Points assigned	Sensitivity (%)	Specificity (%)
Highest serum-IgE level (IU/mL)	More than 2000	10	95.8	3.3
Skin abscesses	More than 4	8	85.4	63.3
Retained primary teeth	More than 3	8	78.6	75
Highest eosinophil count (cells/mL)	More than 800	6	93.5	23.3
Characteristic face	Present	5	95.8	60
Hyperextensibility of joints	Present	4	59.6	76.7
High-arched palate	Present	2	-	-
Total score		43	-	-

cloxacillin, vancomycin, and linezolid. Thus, she was started on intravenous cloxacillin at 50 mg/kg/dose thrice daily for 14 days.

As the child had multiple episodes of soft-tissue abscess, distinctive facial features, and peripheral blood eosinophilia, a possibility of HIES (Job's syndrome) was suspected and she was evaluated for the same. The child's serum IgE levels were significantly elevated: 2260 UI/mL (normal: 150–300 UI/mL) confirming the diagnosis of AD-HIES. Although genetic testing for the presence of STAT3 mutations was planned, it was deferred due to logistic reasons.

DISCUSSION

The HIES or the Job's syndrome is an uncommon, primary immunodeficiency disorder, which is characterized by dermatitis, recurrent pneumonitis, recurrent soft-tissue abscesses, coupled with peripheral eosinophilia, and elevated levels of serum IgE [1]. HIES has two distinct clinical entities, AD-HIES and AR-HIES. The autosomal dominant or the classical hyper-IgE syndrome presents with dental, facial (deep-set eyes, prominent forehead, broad nasal bridge, mild prognathism, and increased inter-alar distance) [1], and connective tissue abnormalities (bone fractures, delayed tooth eruption, hyperextensible joints, and scoliosis) [2]. The AR-HIES lacks these typical features and predominantly presents with viral infections and neurological manifestations [3].

AR-HIES is probably heterogeneous, with more than 1 gene contributing to its etiology. Autosomal dominant forms of disease are associated with mutations in the STAT3 gene, which is found in the majority of cases, whereas the autosomal recessive forms of the disease are associated with mutations in the DOCK8 and the tyrosine kinase 2 genes [4-7]. *STAT3* is involved in various immune mechanisms and its mutation leads to amplification of IgE production by the B-lymphocytes, defective chemotaxis of neutrophils. It also impairs the anti-inflammatory properties of interleukin-10 (IL-10) and IL-6, leading to the deficiency of T-helper 17 cells in Job's syndrome [8].

Most predominant clinical features in HIES include skin abscesses, eczema, drug allergy, and food allergy followed by environmental allergy, retained primary teeth, fractures, scoliosis, and cancer [7,9]. The STAT3 deficiency can be strongly considered when a child/adult manifests with typical facies, internal organs abscesses, severe infections, pneumatoceles, and mucocutaneous candidiasis, scoliosis, and bone fractures alongside increased serum IgE levels [10].

A scoring system was developed by Grimbacher *et al*. to predict the likelihood of HIES genotype based on both clinical and laboratory test criteria. Features which were characteristic to HIES had more points than those which were prevalent not only in HIES but also in the general population. Points varied from 0 to 10 depending on the uniqueness of the clinical or laboratory feature. There were 19 clinical features and two laboratory features (highest serum-IgE level and highest eosinophil count) [3]. It was seen that, as per total point scoring, >15 points suggested likely presence of HIES genotype, 10–14 points showed indeterminate presence, and <10 points suggested unlikely presence of HIES genotype [3].

Some of the clinical features such as typical facial profile, retained primary teeth, and scoliosis are likely to manifest for the 1st time during adolescence. Index case being an adolescent had facial features as well as retained primary teeth. It is seen that, as the child grows older, the frequency of infection, fracture, and pneumatoceles increases. The index case had a total score of 43 as per the scoring system which is likely suggestive of HIES genotype (Table 1). This case is unique in its delayed presentation of recurrent skin abscesses without dermatitis (eczema).

In diagnosed cases of STAT-3 mutations, Schimke *et al*. described the sensitivity and specificity of various clinical features [11]. Increased serum IgE levels (>10 times normal), blood eosinophilia, eczema, pneumonia, and characteristic facies have >90% sensitivity. Skin abscesses and increased susceptibility to infections have sensitivity between 80 and 90%. Pathologic second dentition and rash in neonatal period have sensitivity between 70 and 80%. Positive family history of HIES, internal abscesses, and severe infections have very high specificity (100%). Index case had increased serum IgE levels, blood eosinophilia, and characteristic facies; three out of five features with high sensitivity and positive family history which had 100% specificity [11]. Fan *et al*. reported four cases of HIES aged between 3 and 13 years. A total of three out of four cases had staphylococcal mucocutaneous infection. Only half of them had facial features suggestive of HIES. Serum IgE levels were >2000 in all the four cases [12].

Differential diagnosis of HIES includes atopic dermatitis, severe combined immunodeficiency, Wiskott–Aldrich syndrome, and Netherton syndrome. However, the index case did not have dermatitis and the platelet count and morphology were normal [13-15]. The mainstay of management in children with Job's syndrome is to provide optimum skin care, prompt treatment of infections, and control of pulmonary complications and prevention of infections. Oral cyclosporine, prednisolone, topical calcineurin inhibitors, and phototherapy are contraindicated in these cases due to the impaired innate and adaptive immune responses. Deep-seated abscesses should be aggressively managed in these children with parenteral antibiotics and surgical drainage if necessary. Pus culture and sensitivity patterns need to be strictly followed to guide the therapy against the staphylococcal strain [16].

Intravenous immunoglobulin and interferon-gamma, levamisole, omalizumab, bisphosphonates, and bone marrow transplantation have been used in cases of Job's syndrome, with favorable outcomes [17-19]. Index case was managed with supportive and symptomatic care. She was advised skin care and topical anti-staphylococcal therapy to reduce staphylococcal colonization along with prophylactic trimethoprim-sulfamethoxazole.

CONCLUSION

Although, HIES, a primary immunodeficiency disorder is rare, children manifesting with recurrent skin or soft-tissue

infections should be screened for HIES for timely management of complications and family screening.

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